DISSERTATION ON

STUDY ON ETIOLOGY OF ASCITES

SUBMITTED FOR

M.D. BRANCH-I (GENERAL MEDICINE)

MARCH 2009

THANJVUR MEDICAL COLLEGE,

THANJAVUR

THE TAMILNADU DR.MG.R.MEDICAL UNIVERSITY, CHENNAI.

FOR THE EXAMINATION IN MARCH 2009

CERTIFICATE

This is to certify that this dissertation entitled "STUDY ON ETIOLOGY OF ASCITES" submitted by Dr.R.BHARANIKUMAR, to the faculty of Internal medicine, The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D.Degree Branch-I (Internal Medicine) is a bonafide research work carried out by him under my direct supervision and guidance.

Dr.S.MUTHUKUMARAN, M.D.,
Professor and Head of Department,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur-613004.

Dr.N.JEEVA, M.D.,
Professor of Therapeutics,
Unit Chief,
Thanjavur Medical College,
Thanjavur-613004.

Dr.P.JEYANTHI, M.D.,
The Dean,
Thanjavur Medical College & Hospitals,
Thanjavur-613004.

ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank our Dean, Dr.P.JEYANTHI, M.D., Thanjavur Medical College and our former deans Dr.R.M.NATARAJAN, M.S., Dr.S.BALAKRISHANAN, M.D., for having granted permission to do this dissertation in Thanjavur Medical College.

I am immensely grateful to our beloved professor and HOD. Dr. S.MUTHUKUMARAN, M.D., for his guidance and immense support for this study.

It is with deepest appreciation and gratitude that I thank my unit chief, Dr.N.JEEVA,M.D., Prof. of. Therapeutics, my guide and mentor for maneuvering this study at every meander and without whose able guidance, constant encouragement, this study could not have been possible.

I express my sincere gratitude to my beloved former chief Prof. Dr. G.DHANDAPANI,M.D., for his constant guidance and encouragement in my dissertation work.

I am extremely thankful to Prof. Dr.R.GANESAN,MD.,D.M., chief medical gastroenterologist, Dr.C.KRISHNAN,M.D., D.M., medical gastroenterologist for helping and guiding me thorought my dissertation work.

I sincerely extend my gratitude to all the unit chiefs of department of medicine Prof. Dr. S. PALANIYANDY,M.D., Prof .Dr. P.KRISHANAMOORTHY,M.D., Prof.Dr.D.SWAMINATHAN,M.D., Prof.Dr.A.RAJENDRAN,MD., for allowing me to work on their patients in their wards.

I am thankful to our unit Assistant Professors, Dr.P.KUMAR,M.D., Dr.A.SRINIVASAN,M.D., Dr.R.VIVEKSARAVANAN,M.D., Dr.CAESER,M.D., for their guidance and support. I also thank my unit CRRIs for their help in this study.

I will not be pardoned if I am not thankful to the patients who have participated in this study.

CONTENTS

INTRODUCTION

The term ascites is derived from the greek word "ASKOS" (bladder, belly, bag) and denotes the presence of excessive fluid in the peritoneal cavity. [1]. Many diseases are known to lead to the formation of free fluid within the peritoneal cavity. Basically the causes of ascites may be grouped into those conditions in which the pathological process does not directly affect the peritoneum and those in which the peritoneum itself is involved. The first group includes diseases associated with sinusoidal portal hypertension (cirrhosis, acute alcoholic hepatitis, fulminant or subacute viral or toxic hepatitis, congestive heart failure, constrictive pericarditis, IVC obstruction, Budd-Chiari syndrome, hepatoveno occlusive disease) hypoalbuminaemia (Nephrotic Syndrome, protein-losing enteropathy, and malnutrition), and a variety of disorders that may cause ascites through different mechanisms, such as myxoedema, ovarian diseases (carcinoma, benign tumours, ovarian hyperstimulation syndrome), chronic pancreatitis, biliary-tract leakage (secondary to liver trauma, biliary-tract surgery, or transhepatic cholangiography), diseases affecting the lymphatic system of the splanchnic area and chronic renal failure. In the second group, ascites is formed as a consequence of primary peritoneal disease or as a result of peritoneal involvement in systemic process; tuberculous, fungal (Candida albicans, Coccidioides immitis), parasitic and granulomatous peritonitis (sarcoidosis, Crohn's disease, peritoneal granulomatous reaction to talc, cotton, wood fibers, starch and barium), primary or metastatic peritoneal

tumours, vasculitis (systemic lupus erythematosus, Henoch-Schonlein purpura), eosinophilic gastroenteritis, and Whipples disease are the most characteristic causes of ascites in this group.[2]

The evaluation of a patient with ascites requires that the cause of the ascites to be established. In most cases ascites appears as part of a well recognized illness such as cirrhosis, congestive heart failure, nephrosis or disseminated carcinomatosis, in these situations the physician should determine that the development of ascites is indeed a consequence of the basic underlying disease and not due to the presence of a separate or related disease process. This distinction is necessary even when the cause of ascites seems obvious.

Diagnostic paracentesis (50-100ml) should be part of the routine evaluation of the patient, with ascites. The fluid should be examined for its gross appearance, protein content, albumin level, cell count, and differential cell count, should be determined and gram's and acid fast stains and culture should be performed. Cytologic and cell block examination may disclose an otherwise unsuspected carcinoma. Serum ascites albumin gradient (SAAG) should be calculated to determine whether the fluid has features of a transudate or an exudate. The gradient correlates directly with portal pressure, a gradient >1.1 gm/dl, high gradient ascites is characteristic of uncomplicated cirrhotic ascites and differentiates ascites due to portal hypertension > 97% of the time. Other etiologies of high gradient ascites

include alcoholic hepatitis, congestive heart failure, hepatic metastasis constrictive pericarditis and Budd chiari Syndrome. A gradient < 1.1 gm/dl (Low gradient) suggests that the ascites is not due to portal hypertension with > 97 % accuracy and mandates a search for other causes such as peritoneal carcinomatosis, tuberculous peritonitis, pancreatitis, serositis, pyogenic peritonitis, and nephrotic syndrome.

Blood stained fluid with > 2.5gm / dl protein is unusual in uncomplicated cirrhosis but is consistant with tuberculous peritonitis or neoplasm. Cloudy fluid with predominance of polymorphonuclear cells > 250 / micro liter and a positive Gram's stain are characteristic of bacterial peritonitis, which requires antibiotic therapy, if most cells are lymphocytes tuberculosis should be suspected. Chylous ascites refers to a turbid milky or creamy peritoneal fluid due to presence of thoracic or intestinal lymph. Such fluid shows sudan staining fat globules microscopically and an increased triglyceride content by chemical examination. Opaque milky fluid has a triglyceride concentration > 1000 mg/dl, but a triglyceride Concentration > 200mg is sufficient for diagnosis. A turbid fluid due to leukocytes, or tumor cells may be confused with chylous fluid (pseudochylous) and it is often helpful to carry out alkalinization and ether extraction of the specimen. Alkali tend to dissolve cellular proteins and thereby reduce turbidity, ether extraction leads to clearing if the turbidity of the fluid is due to lipid. Chylous ascites is often the result of lymphatic disruption, or obstruction from cirrhosis, tumor, trauma, tuberculosis, filariasis, or congenital abnormalities. It may also be seen in nephrotic Syndrome.

AIM OF THE STUDY

To study the various Etiologies and their incidence of Ascites.

REVIEW OF LITERATURE

DEFINITION:

Ascites is defined as the accumulation of excess fluid in the peritoneal cavity. Fluid accumulates when it enters the peritoneal cavity from the mesenteries, the peritoneum and hepatic surface at a rate greater than can be returned to the circulation via the capillaries and lymphatics. [1]

ANATOMY OF THE PERITONEUM

The peritoneum is a serous membrane which lines the abdominal cavity; it covers the anterior and posterior walls, the under surface of the diaphragm and the pelvic cavity, All this is the parietal peritoneum. In places it leaves the posterior abdominal wall or diaphragm to form a partial or complete investment for viscera; this is the visceral peritoneum, which forms the serous covering for many viscera.

Peritoneum consists of a single layer of flattened cells, mesothelium, overlying areolar tissue which varies in both thickness and density in different places. Over expansile parts this areolar tissue is loose and cellular (e.g. transversalis fascia on the lower anterior abdominal wall) while over non-expansile parts it is often very thick (eg. Iliac fascia, psoas fascia, parietal pelvic fascia); but loose or dense, thin or thick, these variously named fasciae are part of the one continuous extraperitoneal connective tissue lying between the parietal peritoneum and the walls of the abdominal

and pelvic cavities. On the posterior abdominal wall the dense psoas and iliac fasciae and the anterior layer of the lumbar fascia serve as firm bases upon which the extraperitoneal tissue can gain attachment. The posterior surfaces of retroperitoneal structures (pancreas, duodenum, ascending and descending colon) also gain a firm attachment to these fasciae,. Thus peritoneum and viscera have a firm anchorage undisturbed by the movements of contraction of the underlying muscles.

Various folds or reflections of peritoneum connect viscera to the abdominal walls or to one another. Some of these are properly called folds, but others may be called a mesentery, omentum or ligament, The double fold supporting most of the small intestine is the mesentery; the mesenteries supporting the transverse colon, sigmoid colon and appendix are the transverse mesocolon, sigmoid mesocolon and mesoappendix,. The lesser omentum connects the stomach to the liver, and the greater omentum hangs down from the lower border of the stomach. The various ligaments associated with the liver, stomach and spleen are simply peritoneal folds and bear no relation in structure or strength to the ligaments of muscles and joints; the name as applied to peritoneum is an unfortunate one. A few of these peritoneal structures are easy to see on opening the abdomen through the anterior abdominal wall (e.g. the greater omentum and the mesentery), but others can only be properly appreciated when viscera are displaced or removed.

PERITONEAL CAVITY: GREATER AND LESSER SACS

The serous-coated organs fill the abdominal cavity so that visceral surfaces are in contact with one another or with the parietal peritoneum. The space between them is only potential, not actual, and it contains only a few milliliters of tissue fluid which lubricates adjacent surfaces so they can slide over one another, this is the general peritoneal cavity, body cavity or coelom, and is opened up when incisions that include parietal peritoneum are made through the abdominal wall. Another name for it is the greater sac.

The lesser sac properly called the omental bursa, is a diverticulum of the peritoneal cavity behind the stomach. It exists because of the way the liver, stomach and spleen change their positions and shapes during development, and its purpose is to provide a slippery surface for the necessary mobility of the posterior surface of the stomach. It opens into the greater sac through a slit-like aperture in front of the inferior vena cava, the epiploic foramen.

Theoretically the cavity of the lesser sac should extend down between the layers of the greater omentum but because of the fusion of layers it rarely extends much below the stomach, the lesser omentum and stomach form the anterior wall of the sac to the left the sac extends to the hilum of the spleen where the peritoneum forms the lienorenal and gastrosplenic ligaments, while at its right edge is the epiploic foramen, also described below with the lesser omentum. The sloping roof of the sac is the peritoneum covering the caudate lobe of the liver and this is continuous with the peritoneum of the posterior wall which overlies part of the diaphragm, pancreas, left kidney and

suprarenal gland. The lowest part of the posterior wall is the transverse mesocolon, attached to the lowest part of the pancreas Many of these posterior wall features can only be properly understood when this region of the posterior abdominal wall and its associated structures have been considered, but some further details should be noted now.

A finger introduced through the epiploic foramen cannot explore the whole of the lesser sac, but some features are palpable. Behind the posterior wall to the left of the inferior vena cava is the aorta, here giving off the coeliac trunk, two of whose branches may be felt. The common hepatic artery curves down to the right behind the peritoneum and then turns up behind the first inch of the duodenum to enter the lesser omentum. It raises the pancreatiocoduodenal fold, which can be felt to the left of the fold the finger tip passes steeply downwards behind the pylorus, as if over a step. The left gastric artery runs up towards the oesophageal opening to enter the lesser omentum on its way up it raises the palpable pancreaticogastric fold. These two folds together produce a slight hourglass constriction of the sac beyond which the cavity becomes extensive, but the examining finger cannot reach its limits.[3]

PHYSIOLOGY OF PERITONEUM

Peritoneum is a complex serous membrane which lines the abdominal wall and is reflected over the viscera within the abdomen. The parietal and

visceral layers are developed respectively, from the somatopleural and splanchnopleural layers of the lateral plate mesoderm.

The total area of the peritoneal surface in the adult is between 1.5 and 2m ^{2} approximately equal to the toal body surface area. The blood flow to the peritoneum is 50-70 ml/mt.

The normal peritoneum consists of a single layer of flattened mesothelial cells, microvilli protrude from the free mesothelial surface which is lubricated by a small column of serous fluid, In women of reproductive age the amount of fluid varies, being greatest during the leuteal phase, If the ovaries are inactive the volume is 4ml only .[4]

CLASSIFICATION AND CAUSES OF ASCITES

Ascites causes may be classified in two ways. Basically the causes of ascites may be grouped into those conditions in which the pathological process does not directly affect the peritoneum and those in which the peritoneum itself is involved. Otherwise ascites can also be classified according to the high gradient and low gradient concept. By the first method ascites can be classified as follows.

CAUSES OF ASCITES [2]:

(I) ASCITES NOT ASSOCIATED WITH PERITONEAL DISEASE:

a. Intra-hepatic sinusoidal portal hypertension

    i. Cirrhosis
    ii. Acute alcoholic hepatitis
    iii. Fulminant hepatitis (toxic or viral)
    iv. Sub-acute hepatitis (toxic or viral)
    v. Hepatic veno-occlusive disease
    vi. Massive liver metastasis
b. Extra-hepatic sinusoidal portal hypertension
    i. Congestive heart failure
    ii. Constrictive pericarditis
    iii. Inferior vena-caval obstruction
    iv. Hepatic vein obstruction (budd-chiari syndrome)
c. Hypoalbuminemia
    i. Nephrotic syndrome
    ii. Protein losing enteropathy, Malnutrition
d. Miscellaneous disorders
    i. Myxoedema
e. Ovarian disease
    i. Carcinoma
    ii. Benign tumours
    iii. Ovarian hyperstimulation syndrome
f. Pancreatic ascites
g. Bile ascites
h. Chylous ascites
i. Nephrogenic ascites

j. Acquired immunodeficiency syndrome

(II) ASCITES DUE TO PRIMARY PERITONEAL DISEASE:

a. Malignant ascites:
    i. Primary peritoneal mesothelioma
    ii. Secondary peritoneal carcinomatosis
b. Granulomatous peritonitis:
    i. Tuberculous peritonitis
    ii. Chlamydia trachomatis peritonitis
    iii. Fungal and parasitic peritonitis (Candida albicans, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, Schistosoma mansoni, Strongyloides stercoralis, Entamoeba histolytica)
    iv. Sarcoidosis
    v. Starch granulomatous peritonitis
    vi. Barium peritonitis
    vii. Vasculitis (SLE, Henoch schonlein purpura)
c. Miscellaneous peritoneal disease:
    i. Eosinophilic gastro-enteritis
    ii. Whipple's disease, Endometriosis

CLASSIFICATION OF ASCITES BASED ON HIGH GRADIENT AND LOW GRADIENT CONCEPT

1. HIGH GRADIENT ASCITES

A. Hypoalbuminaemia

- Nephrotic syndrome
- Protein loosing enteropathy

B. Venous Hypertension

1. Poor return of blood to Right side of heart

Eg.
- Congestive Heart Failure
- Tricuspid regurgitation
- Constrictive pericarditis

2. Blockage of Hepatic veins and / or Venacava

- Budd Chiari Syndrome
- Venoocclusive disease

C. Portal vein obstruction

D. Diffuse Hepatic disease with portal hypertension.

- All forms of cirrhosis

E. Infiltrative process of Liver

- Tumours,
- Lymphoma.
- Granulomatous diseases

II. LOW GRADIENT ASCITES

A. Inflammatory diseases of the peritoneum

Eg. - Ruptured viscus with or without an Intraabdominal sepsis

- Tuberculosis
- Bacterial peritonitis
- Pancreatitis
- Bile peritonitis

B. Malignancy:

- Metastasis to liver or peritoneum
- Hepatocellular carcinoma
- Cholangio carcinoma
- Primary mesothelioma

C. CHYLOUS ASCITES:

- Trauma to Thoracic duct
- Filariasis
- Mediastinal tumors

PATHOGENESIS

BODY FLUID DISTRIBUTION:

Of the total fluid in the human body two-thirds reside inside the cell (i.e intracellular fluid) and one-third resides outside the cell (i.e extracellular fluid). The patient with generalized edema has an excess of ECF. The ECF resides in two locations: in the vascular compartment (plasma fluid) and between the cells of the body, but outside the vascular compartment (interstitial fluid). In the vascular compartment approximately 85% of the

fluid resides on the venous side of the circulation and 15% on the arterial side.

STARLING'S LAW:

It states that the rate of fluid movement across a capillary wall is proportional to the hydraulic permeability of the capillary, the transcapillary hydrostatic pressure difference, and the transcapillary oncotic pressure difference[5].

PATHOGENESIS OF ASCITES IN CIRRHOSIS OF LIVER:

To explain the initiating event three theories have been proposed.

The Underfilling theory:

This suggests that the primary abnormality is the inappropriate sequestration of fluid within the splanchnic vascular bed due to portal hypertension and a consequent decrease in the effective circulating blood volume. The apparent decrease in the intravascular volume (under filling) is sensed by the kidney, which responds by retaining salt and water.

The overflow theory:

Suggests that the primary abnormality is inappropriate renal retention of salt and water in the absence of volume depletion.

The peripheral arterial vasodilatation theory:

According to this theory, portal hypertension results in splanchnic, arteriolar vasodilation leading to underfilling of the arterial vascular space and baroreceptor mediated stimulation of renin-angiotensin sympathetic out put and antidiuretic hormone release.

Regardless of the initiating event a number of factors contribute to accumulation of fluid in the abdominal cavity. Increased central sympathetic outflow is found in patients with cirrhosis and ascites. This results in diminished natriuresis by activation of renin-angiotensin system and diminished sensitivity to atrial natriuretic peptide. Portal hypertension plays an important role by raising hydrostatic pressure within the splanchnic

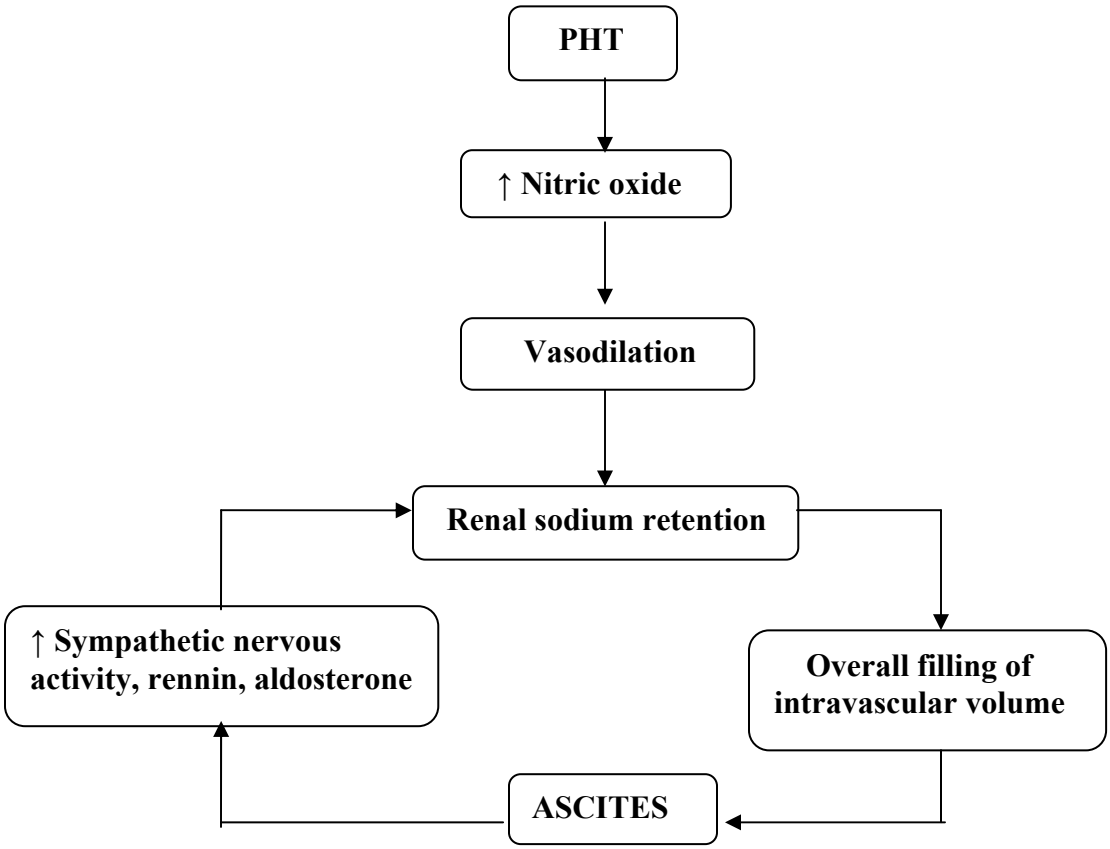
capillary bed. Hypoalbuminemia and reduced plasma oncotic pressure also favour the extravasations of fluid from plasma to the peritoneal cavity.

Hepatic lymph may weep freely from the surface of the cirrhotic liver due to distortion and obstruction of the hepatic sinusoids and lymphatics and contribute to ascites formation.[8]

To summarize, the presence of portal hypertension contributes to the development of ascites in patients who have cirrhosis. There is an increase in intrahepatic resistance, causing increased portal pressure, but there is also vasodilatation of the splanchnic arterial system, which in turn results in an increase in portal venous inflow. Both of these abnormalities result in increased production of splanchnic lymph. Vasodilating factors such as nitric oxide are responsible for the vasodilatory effect. These hemodynamic changes result in sodium retention by causing activation of the renin-angiotensin-aldosterone system with the development of hyperaldosteronism. The renal effects of increased aldosterone leading to sodium retention also contribute to the development of ascites. Sodium retention causes fluid accumulation and expansion of the extracellular fluid volume, which results in the formation of peripheral edema and ascites. Sodium retention is the consequence of a homeostatic response caused by underfilling of the arterial circulation secondary to arterial vasodilatation in the splanchnic vascular bed. Because the retained fluid is constantly leaking out of the intravascular compartment into the peritoneal cavity, the sensation of vascular filling is not achieved, and the process continues.

Hypoalbuminaemia and reduced plasma oncotic pressure also contribute to the loss of fluid from the vascular compartment into the peritoneal cavity. Hypoalbuminaemia is due to decreased synthetic function in a cirrhotic liver [6].

Pathogenesis of Ascites in portal hypertension



Cirrhosis and Its Complications:

Cirrhosis is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening. In the past, it has been thought that cirrhosis was never

reversible; however, it has become apparent that when the underlying insult that has caused the cirrhosis has been removed, there can be reversal of fibrosis. This is most apparent with the successful treatment of chronic hepatitis C; however, reversal of fibrosis is also seen in patients with hemochromatosis who have been successfully treated and in patients with alcoholic liver disease who have discontinued alcohol use.

CAUSES OF CIRRHOSIS :

Alcoholism

Chronic viral hepatitis

- Hepatitis B
- Hepatitis C

Autoimmune hepatitis

Nonalcoholic steatohepatitis

Biliary cirrhosis

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Autoimmune cholangiopathy

Cardiac cirrhosis

Inherited metabolic liver disease

- Hemochromatosis
- Wilson's disease
- α1 Antitrypsin deficiency
- Cystic fibrosis

Cryptogenic cirrhosis.

MALIGNANT ASCITES

Most metastatic tumours originate from adenocarcinomas but lymphoid or myeloid tumors can also infiltrate the peritoneum. Tumors responsible for malignant ascites are many. The most frequent are pancreas, ovary, colon. Ascites may develop for a number of reasons - peritoneal carcinomatosis (2/3 cases), massive liver secondaries, or chylous ascites. Widespread implanation of tumor nodules on the serosal surfaces of Viscera is often found. The pathophysiologic mechanisms of malignant ascites is poorly understood. Mechanism of fluid retention in patients with malignant related ascites may depend on the location of the tumor. Alterations in peritoneal capillary permeability may further provoke ascites formation. It is also suggested that there can be exudation of proteinaceous fluid from tumor cells lining the peritoneum and extracellular fluid enters the peritoneal cavity to reestablish oncotic pressure.

Ascites in patients with primary hepatocellular carcinoma is almost always Secondary to portal hypertension. Chylous ascites due to malignant lymphoma appears to be caused by lymphnode obstruction by tumor and rupture of chyle containing lymphatics.

The macroscopic appearance of malignant ascites is generally similar to that of cirrhotic ascites. Thus the differential diagnosis must be based on exploratory findings and laboratory tests. Measurement of total protein concentration of the ascitic fluid (generally over 3.0 gms/dl in malignant ascites) and its cytological examination for the malignant cells which were

the laboratory tests first used to differentiate malignant ascites from that secondary to portal hypertension are still the most common methods used.

Standard cytological examination is 60 to 90% accurate in the diagnosis of malignant ascites, especially when adequate volumes of fluid (atleast several hundred milliliters) and concentration techniques are used. False positive results are rare in skilled hands. The greatest source of confusion is the differentiation of the malignant cells from atypical mesothelial cells. The use of immunocytochemical techniques with monoclonal or polyclonal antibodies against numerous tumour markers [oestrogen and progesterone receptors, cancer antigen 125, carbohydrate antigen 19_9, carcino-embryonic antigen, epithelial membrane antigen, human erythrocyte antigen , CD15, CD45, CD11c, epithelial glycoprotein 34, BW-495, tumour associated antigen 72, epithelial specific tumour associated monoclonal antibody (Moab), cytokeratin, vimentin, lysozyme and 83D4 antigen] are useful in differentiating malignant from non-malignant ascites in these cases. These techniques may also help differentiate primary (mesothelioma) from metastatic peritoneal malignancy. False negative results on cytological examination are the rule when the ascites is due to portal hypertension secondary to massive liver metastasis with little peritoneal involvement. In this type of ascites the total ascitic protein concentration is usually lower than 2.5 gms/dl. The differential diagnosis between cirrhotic ascites and the ascites secondary to massive liver metastasis, however, can easily be achieved by ultrasonography, computed tomography or liver scan. DNA analysis by flow cytometry or image analysis,

and the detection of oncogene (c-Ha-ras) expression, are sophisticated techniques that have been explored in the differential diagnosis of effusion samples, but they do not improve the results obtained with conventional cytlogical examination.

The serum ascitic fluid gradient for albumin improves the diagnostic accuracy of total protein concentration in the ascitic fluid. The concentration of lactic dehydrogenase in malignant ascites is higher than the corresponding values in plasma due to leakage of enzymes from the malignant cells lining the peritoneum, whereas the reverse is the rule of cirrhotic ascitis. The concentration of lactic dehydrogenase in ascitic fluid and its ascitic fluid-plasma ratio are, therefore, useful for differentiating malignant from cirrhotic ascites, although they do not improve the results obtained with the ascitc fluid-plasma albumin gradient. Other measurement in ascitic fluid that have proved to be of value in differentiating malignant from cirrhotic ascites include total lipids, free fatty acids, cholesterol, fibro-nectic, carcino-embryonic antigen and other tumour-associated antigens, urokinase, tissue plasminogen activator, plasminogen activator inhibitor, fibrin/fibrinogen degradation products and human chorionic gonadotropin-β. Of these last, the cholesterol concentration of ascitic fluid, which is higher in most malignant ascites than in cirrhotic ascites owing to higher permeability to lipoproteins, seems to the most interesting because of its simplicity and cost-effectiveness. Laproscopy and direct biopsy of the peritoneal metastasis is a useful approach to confirm the diagnosis of malignant ascites in those cases with negative cytology [2].

Classification of malignancy related Ascites

Peritoneal carcinomatosis,

Massive Liver metastasis

Peritoneal carcinomatosis with massive liver metastasis

Hepatocellular carcinoma

Malignant lymphnode obstruction

Malignant Budd- Chiari Syndrome (tumor emboli in hepatic veins) [8] .

ASCITES IN CARDIAC FAILURE:

Heart failure is a clinical syndrome in which an abnormality of cardiac structure or function is responsible for the inability of the heart to eject or fill with blood at a rate commensurate with the requirements of the metabolizing tissues. Heart failure results in a constellation of clinical manifestations, including, in various combinations, circulatory congestion, dyspnoea, fatigue, and weakness. Heart failure is frequently but not always, caused by a defect in myocardial contraction, and then the term myocardial failure is appropriate.

Etiology:

Two mechanisms that reduce cardiac output are recognized to cause congestive heart failure; systolic dysfunction and diastolic dysfunction. Although physical examination, chest x-ray, and echocardiogram are useful in this regard, additional diagnostic tests are usually indicated. An electrocardiogram provides information about systolic (ejection fraction) and diastolic function, and about vascular disease which may require surgery. Occult hypo- or hyperthyroidism and alcoholic cardiomyopathy may present as congestive cardiac failure; these are treatable.

Ascites occurs in patients with increased pressure in the hepatic veins and in the veins draining the peritoneum. Ascites usually reflects the long standing systemic venous hypertension. In patients with organic tricuspid valve disease and chronic constrictive pericarditis ascites may be more prominent than subcutaneous edema.

Protein losing enteropathy may rarely occur in patients with visceral congestion or end stage congenital heart disease, and the resultant reduced plasma oncotic pressure may lower the threshold for the development of ascites [9].

NEPHROTIC SYNDROME:

Another major cause of edema is nephrotic syndrome, the clinical hallmarks of which include proteinuria (>3.5 gms/day), hypoalbuminemia, hypercholesterolemia and and edema. The degree of edema may range from pedal edema to total body anasarca, including ascites and pleural effusions. The lower the plasma albumin concentration , the more likely the occurrence of anasarca; the degree of sodium intake is, however also a determinant of the degree of edema.

The nephrotic syndrome is a clinical complex charecterised by a number of renal and extra- renal features, the most prominent of which are proteinuria of more than 3.5gms/1.73m^2/24hrs, hypoalbuminemia, edema, hyperlipidemia, lipiduria and hypercoagulability. Nephrotic syndrome can complicate any disease that perturbs the negative electro-static charge or architecture of the GBM and the podocytes and their slit diaphragms. Recent attention has focused on several key molecules that mediate GBM-podocyte-slit diaphragm interactions such as nephrin, podocin and alpha actinin-4. Six entities account for more than 90% cases of nephrotic syndrome in adults. Minimal change disease , focal and segmental glomerulosclerosis (FSGS),

membranous glomerulopathy, membranoproliferative glomerulonephritis, diabetic nephropathy and amylodosis.

Pathophysiology:

The pathogenesis of ECF volume expansion in nephrotic syndrome appears to be due to primary renal Na retention causing nephrotic edema.

In general the greater the proteinuria, the lower the serum albumin level. Hypoalbuminemia is compounded further by increased renal catabolism and inadequate, albeit usually increased hepatic synthesis of albumin. The pathophysiology of edema in nephrotic syndrome is poorly understood. The underfilling hypothesis postulates that hypoalbuminemia results in decreased intravascular oncotic pressure leading to leakage of extracellular fluid from blood into interstitium. Intravascular volume falls, thereby stimulating activation of renin-angiotensin-aldosterone axis and the sympathetic nervous system and release of vasopressin and suppressing atrial natriuretic peptide release. These neural and hormonal responses promote renal salt and water retention, thereby restoring intravascular volume, and triggering further leakage of fluid into interstium. Primary renal salt and water retention also contributes to edema formation in some cases.

It appears, therefore, that nephrotic syndrome reflects a combination of primary renal NaCl retention and relative arterial underfilling. In general, normal or near normal glomerular filtration rate is associated with hypovolemic, vasoconstrictive nephrotic syndrome, whereas a diminution in glomerular filteration rate, primary renal sodium retention, and evidence of

volume expansion (e.g., decreased plasma renin activity) are characteristic of hypervolemic nephrotic syndrome [10].

TUBERCULOUS PERITONITIS:

The differential diagnosis between cirrhotic ascites and ascites due to tubercular peritonitis is particularly important since alcoholic cirrhosis may predispose to peritoneal tuberculosis. Clinically, tuberculous peritonitis is characterized by fever, abdominal pain, anorexia, weight loss, abdominal tenderness and ascites. However, none of these symptoms is invariably present. The proportion of the patient with pleural or pulmonary tuberculosis or with a reactive tuberculin skin test ranges between 21 and 78% and between 30 and 89% respectively. In females without active tuberculosis, peritoneal tuberculosis may represent the local extension of tuberculous salphingitis. However in many cases no active focus of tuberculosis, apart from the peritoneal disease, can be detected. Ultrasonography and computed tomography may suggest the diagnosis of tuberculous peritonitis. Findings frequently seen in tuberculous peritonitis include diffuse, regular peritoneal thickening, infiltration of greater omentum, ascites with fine, mobile septations or floating debris on ultrasonography, loculations of ascites, bowel thickening, particularly in ileo-caecal area, retro-peritoneal lymph node enlargement, lesions in solid organs (pelvic , adrenal, hepatic, splenic), cold abscesses and adhesions.

Results of examination of the peritoneal fluid are also suggestive of tuberculous infection if there is an increased concentration of protein (>3gms/dl) and lymphocytes. However, it has been shown that the ascitic fluid may be a transudate, particularly in cirrhotics with ascites and tuberculous peritonitis. Ziehl-nielsen stained smears usually fail to show acid

fast bacilli. The proportion of cultures of ascitic fluid positive for Mycobacterium tuberculosis varies markedly from series to series (from 8-69%) probably reflecting technical differences. It has been suggested that the proportion of positive cultures may be increased upto 80% by concentrating 1 litre of the fluid by centrifugation. Nevertheless, the diagnosis of tuberculous peritonitis cannot be based on cultures of ascitic fluid since the usual techniques of culturing acid fast bacilli may require several weeks to obtain a definite result. The activity of lactic dehydrogenase in ascitic fluid is greater in tuberculous peritonitis than cirrhosis. As in malignant ascites, the concentration of this enzyme in tuberculous ascites is higher than in plasma. There are reports that the concentration of tumour antigens CA-125 in ascitic fluid may be very high in tuberculous peritonitis. The activity of adenosine deaminase in the peritoneal fluid is provenly sensitive and specific test for tuberculous peritonitis. This is an enzyme in the catabolism of purine bases. It participates in the proliferation and differentiation of lymphocytes, and increases in tuberculous effusions probably as a consequence of the stimulation of cell mediated immunity and T- lymphocytes. The iso-enzyme adenosine deaminase II is a dominant component of tuberculous pleural effusions. The concentration of interferon γ in ascitic fluid is also greater in tuberculous peritonitis than cirrhotic ascites, although this does not improve on the results obtained with adenosine deaminase in the diagnosis of this condition. The concentration of adenosine deaminase in ascitic fluid in tuberculous peritonitis correlates directly with the total protein concentration in ascites. It is therefore not surprising that

the number of false negative results for adenosine deaminase in tuberculous peritonitis is higher in cirrhotic patients than in patients without chronic liver disease.

Open peritoneal biopsy during a laparotomy or a mini-laparotomy, blind needle biopsy of the peritoneum, and laparoscopy with direct biopsy of the affected areas have been used to confirm the diagnosis of tuberculous peritonitis. Laparoscopy with direct peritonel biopsy is the best of these methods. The peritoneum characteristically shows scattered or confluent military nodules of uniform size, with adhesions between bowel loops, liver capsules and abdominal walls. The histological appearance is characterized by the presence of caseating granulomas. In some instances, tubercle bacilli may be seen by staining with auramine rhodamine and microscopy under ultra-violet light. Mycobacterium tuberculosis can be cultured from the biopsy specimen of the peritoneum. The macroscopic and microscopic appearances of tuberculous peritonitis are similar to those of other conditions causing granulomatous peritonitis, such as sarcoidosis, crohn's disease, and iatrogenic granulomatous peritonitis. The last condition occurs after 0.15% of abdominal operations and is usually caused by a cell mediated immune response to starch, talc, cotton fibres, wool fibres originating from disposable surgical gowns and drapes. Iatrogenic granulomatous peritonitis appears 2-9 weeks post-operatively and is charecterised by abdominal pain, tenderness and fever, and frequently by accumulation of ascites. The observation of starch granules in the ascitic fluid obtained by paracentesis can be diagnostic [2].

PANCREATIC ASCITIS:

Pancreatic ascites occurs in approximately 3% of patients with chronic pancreatitis as a result of leakage of fluid from ruptured pancreatic duct, or from a pancreatic pseudo-cyst into the peritoneal cavity. Other less frequent causes include acute hemorrhagic pancreatitis, abdominal trauma and pancreatic cancer. Since most patients with chronic pancreatitis are alcoholics and may develop massive ascites with little or no abdominal tenderness, the differential diagnosis of pancreatic from cirrhotic ascites may be difficult on clinical grounds. Laboratory analysis are therefore essential to establish a correct diagnosis. In virtually all cases, serum and especially ascitic fluid amylase and lipase are dramatically increased. The concentration of pancreatic enzymes in ascitic fluid is between 5 and 20 times greater than the plasma concentrations obtained simultaneously. The protein concentration in ascitic fluid is generally over 3gms/dl and the fluid is usually serous, but can be sero-sanguineous, turbid, chylous. The concentration of methaemalbumin in ascites is markedly increased in patients with haemorrhagic pancreatitis and has prognostic significance. The concentration of leucocytes in ascitic fluid ranges between 70 and 2200/mm^3, 80% being lymphocytes. Ultrasonography or computed tomography are important diagnostic procedures for pancreatic ascites since they may detect the presence of pseudo-cyst. Pseudo-cyst in patients with pancreatic ascites are usually small, due to continuous leakage of the cyst fluid into the peritoneal space [11].

BUDD - CHIARI SYNDROME:

This syndrome comprises of Hepatomegaly, Abdominal pain, Ascites, Zone 3 sinusoidal distension and pooling. Arise from obstruction to hepatic veins at any site from the efferent vein of the acinus to the entry of the inferior vena cava into the right atrium.

Constrictive pericarditis or right heart failiure – produce a similar syndrome.

Associated clinical conditions :

Myeloproliferative diseases (polycythemia rubra vera)

Systemic lupus erythematosus.

Disseminated intravascular coagulation.

Antiphospholipid syndrome.

Idiopathic granulomatous venulitis

Deficiency of anticoagulant factors – antithrombin III , protein C or S deficiency.

Paroxysmal nocturnal haemoglobinuria

Risk factors :

Oral contraceptives

Pregnancy

Trauma in those with hypercoagulable state.

Liver transplantation and cellular rejection.

In Neoplasm:

Secondary to thrombosis in malignant disease – adrenal ca., renal ca.,

Invasion by hepatocellular carcinoma.

Angiosarcoma, leiomyosarcoma of the hepatic veins.

Testicular lesions metastatic to the right atrium.

Wilms tumour metastasis [12].

OTHER TYPES OF ASCITES:

Other causes of ascites is easily differentiated from cirrhotic ascites include nephrogenic ascites, myxoedema, and Meig's syndrome. The pathogenesis of ascites in these patients is unknown. The protein concentration in ascitic fluid is usually over 3.0gms/dl and WBC count ranges between 30 and 1500/mm3. The amylase and lactic dehydrogenase activities in ascitic fluid are lower than the plasma concentration.

High protein ascites may develop in patients with Acquired immunodeficiency syndrome in the absence of portal hypertension or any other potential cause of ascites [2].

ASCITES CLINICAL FEATURES AND DETECTION

Abdominal distension is a common problem in clinical medicine and may be the initial manifestation of a systemic disease or of otherwise unsuspected abdominal disease.

Pain is uncommon in ascites due to cirrhosis, but when it is present, pancreatitis, hepatoma or spontaneous bacterial peritonitis should be considered.

Inspection of the abdomen is an important aspect of the abdominal examination. By noting abdominal contour, one may be able to distinguish localized from generalized swelling. The tensely distended abdomen with tightly stretched skin, bulging flanks and everted umbilicus is characteristic of ascites.

Other associated features which may be present are hernia, abdominal striae, divarication of recti and occasionally meralgia paraesthetica, and scrotal oedema.

Prominent abdominal venous pattern with the direction of flow away from the umbilicus often is a reflection of portal hypertension. Venous collaterals from the lower part of the abdomen towards the umbilicus suggest obstruction of Inferior venacava [13].

Pleural effusions can be found in 10% of patients usually on the right side.

On examination small amounts of fluid may be difficult to detect in obese patients. Patients usually have flank dullness to percussion and shifting dullness. Approximately 1500ml, of fluid is required to cause flank dullness [14].

If no flank dullness is present the patient has less than 10% chance of having ascites. Eliciting periumbilical dullness with the patient on hands and knees what is known as Puddle sign can detect fluid as little as 120ml in quantity. But the sensitivity and specificity of the puddle sign in detecting ascites have been found to be much lower than those of shifting dullness.

A venous hum at the umbilicus may signify portal hypertension and an increased collateral blood flow around the liver.

A very hard or nodular liver is a clue that the liver is infiltrated with tumor and when accompanied by ascites, it suggests that the latter is due to peritoneal seeding. The presence of a hard periumbilical nodule (sister Mary Joseph's nodule) suggests, metastatic disease from a pelvic or gastrointestinal primary.

The neck veins of the patients with ascites should always be examined specifically. Constrictive pericarditis is one of the few curable causes of ascites. A pulsatile liver and ascites may be found in tricuspid regurgitation [13].

INVESTIGATIONS AND DIFFERENTIATING CAUSES OF ASCITES

The diagnosis of the causes of ascites formation is based on the results of history, physical examination and ascitic fluid analysis and other investigations.

INVESTIGATIONS

PLAIN RADIOGRAPH OF THE ABDOMEN

In the presence of ascites there is generalized hazy appearance with loss of density and detail, particularly at the hepatic angle, and obliteration of the psoas shadow. Supine and lateral views show the gut to be floating on fluid. But the plain radiograph is useful in only less than 50% patients [4].

ULTRASONIC SCAN

This technique is sensitive and can detect as little as 100-300ml of fluid, but the technique is highly dependent on the operator.

Early features on the scan are free fluid in the superior right paracolic gutter, lateral to the liver or in the pelvis. As fluid accumulates, it is detected around and beneath the liver and in the lesser sac, the transverse colon floats on the surface of the mesentry. The bowel has a characteristic polycystic or arcuate appearance.

The features of transudate in ultrasound scan are homogenous echo free areas surrounding and interposed between the loops of bowel and the viscera in an uniform manner. The features of an exudates are small amorphous echoes, septa and matted loops of bowel, Upper abdominal ultrasound also allows screening of the liver, spleen, pancreas, and kidney for disease [6].

ULTRASOUND IN CIRRHOSIS AND PORTAL HYPERTENSION

The sonographic changes in hepatic size and tissue texture is observed in patients with cirrhosis. Nevertheless cirrhosis should be suspected if decreased hepatic size, nodularity of liver surface, accentuation of the fissures, marked coarsening of the hepatic architecture, regenerating nodules, ascites or signs of portal hypertension are seen. The reported sensitivity of ultrasound in the diagnosis of cirrhosis based on hepatic architecture was between 65% and 95%.

Sonography has an important role in the detection of portal hypertension and in the non-invasive evaluation of the portosystemic collateral circulation.

Measuring portal vein size and observing respiratory variations in the superior mesenteric and splenic veins are simple and sensitive methods for detecting portal hypertension. The diameter of the portal vein in normal individual ranges from 0.64 to 1.2 cm and the mean diameter is 1.2 cm in cirrhotic patients. There is a significant correlation between the diameter of the portal vein and maximal spleen length and the magnitude of varices seen endoscopically. A portal vein diameter larger than 1.3 cm is 100% specific for portal hypertension but is seen in only 75% of cases. Other important sign of portal hypertension is the disappearance of the normal splenic and mesenteric vein caliber variation with respiration, which occur in 78.5% and 88.4% of patients respectively.

Lack of distensibility of the portal vessels with respiration is an important sign. In normal individuals the portal venous system distends with deep inspiration and breathholding because of diphargmatic descent and compression of hepatic venous outflow. Indeed the diameter of the splenic vein or superior mesenteric veins may increase upto 50-100%. Ninety percent of the patients with manometrically proven portal venous system is already maximally distended and the respiration induced pressure changes are poorly transmitted through the scarred liver [15].

COMPUTED TOMOGRAPHY

This technique accurately detects small volumes of fluid, particularly with in the pelvic, perihepatic or perisplenic regions. It is of particular help in the diagnosis of intra abdominal masses associated with ascites, to delineate the retroperitoneal area and to diagnose haemoperitoneum.

Other investigations which may provide diagnostic help include upper GI endoscopy, laparoscopy and peritoneal biopsy.

ASCITIC FLUID ANALYSIS

Ascitic fluid is obtained by abdominal paracentesis.

Abdominal Paracentesis

Abdominal paracentasis with appropriate ascitic fluid analysis is probably the most rapid and cost effective method of diagnosing the cause of ascites. There are few contraindications to paracentesis, Coagulopathy is a

potential contraindications. Coagulopathy should preclude paracentesis only when there is clinically evident disseminated intravascular coagulation.

The only prospective study published[16] regarding paracentesis complications in patients with ascites documented no death or infections caused by the paracentesis, there were no episodes of haemoperitoneum or bowel entry by the paracentesis needle. Complications included only 2 (0.9%) transfusion requiring abdominal wall haematomas and 2 (0.9%) small hematomas in 229 patients despite the fact that > 1% of the patients had an abnormal prothrombin time of which 21% had a prolonged prothrombin time of 5 Seconds or more. A continuation of this study involving more than 1500 paracentesis has confirmed the safety reported in the initial smaller study (Runyon, Unpublished observations) [16].

Procedure

Patients with large volume ascites can be successfully tapped in the supine position with the head of the bed or examining table slightly elevated, patients with less fluid should be placed in the lateral decubitus positon. Sterile gloves should be used when actually obtaining the fluid. The skin and subcutaneous tissue should be infiltrated with a local anaesthetic after preparing the skin with an iodine solution.

In order to prevent leakage of fluid after the needle is withdrawn, the needle is inserted using a Z tract [12].

ASCITIC FLUID ANALYSIS

GROSS APPEARANCE [8]

Cirrhosis-straw coloured or bilestained.

Neoplasm-straw coloured, hemorrhagic, mucinous or chylous.

Tuberculous peritonitis–clear, turbid, hemorrhagic or chylous

Pyogenic peritonitis – Turbid or purulent.

Congestive heart failure – straw coloured.

Nephrosis-straw coloured or chylous

Pancreatic ascites-Turbid, hemorrhagic or chylous

Cellcount

The mean white cell count in the uncomplicated cirrhotic ascites is reported to be 281 ± 25 cells/mm3. The upper limit is said to be 500 cells/ mm3. However during diuresis in paitents with cirrhosis and ascites, the cells can concentrate to more than 1000 cells/mm3.

The upper limit of absolute PMN leukocyte count in uncomplicated cirrhotic fluid is usually stated to be 250 cells/mm3. Spontaneous bacterial-peritonitis is the most common cause of elevated ascitic WBC count [12].

If mononuclear cells predominate in a raised ascitic white cell count, tuberculosis, neoplasm, and pancreatic ascites should be considered. The presence of candida in the absence of peritoneal dialysis suggests intestinal perforation [6].

The PMN count may be elevated in ascites caused by peritoneal carcinomatiosis, as in that associated with tuberculous peritonitis presumably

because dying tumor cells and tubercles can attract neutrophils into the fluid and may lead to misdiagnosis of SBP [11].

Ascitic Fluid pH

Ascitic fluid in patients with bacterial peritonitis may have a low pH ranging from 7.21-7.31 in contrast to normal range of 7.38-7.58. But the finding is not sufficiently consistent to be a reliable sign of infected ascites claims that an ascitic fluid pH of 7.34 or less or an arterial ascitic fluid pH gradient of 0.1 or more is of diagnostic value have not been substantiated [4].

Gram Stain

Gram stain demonstrate bacteria only when more than 10,000 bacteria /ml of fluid are present. It should be remembered that the median colony count of bacteria in SBP is only 1 organism /ml. Thus sensitivity of gram stain of ascitic fluid in detecting SBP is less than 10% of specimens [11].

Bacteria are found by Gram staining only during overwhelming infection, as in advanced SBP or asplenic pneumococcal sepsis. The gramstain of ascitic fluid is most helpful in detecting free perforation of gut into ascites where sheets of many different bacteria are found.

CULTURE:

The technique of ascitic fluid culture has undergone a dramatic change based on recently published data 17, 18. The most common bacterial infection of ascitic fluid, spontaneous bacterial peritonitis, is monomicrobial with a very low bacterial concentration i.e. medial colony count of one organism per ml. The method of culturing ascitic fluid as if it were urine or stool is predictably insensitive in detecting low colony count monomicrobial infection. It is predictable that culturing ascitic fluid as if it were blood would yield high results.

Inoculating 10-20 ml of fluid per bottle of a pair of 100ml. aerobic and anaerobic bottle appears to optimize yield,. So the ascitic fluid to culture medium ratio is 1:5 to 1:10, same as for blood culture.

In the studies that have been published conventional cultures have been found to detect bacterial growth in 42-43% of samples of neutrocytic ascites. Where as beside inoculation of blood culture bottle with ascitic fluid detects growth in 91-93%.

The direct smear of ascitic fluid for detection of mycobacteria is almost never possible because low concentration of mycobacteria in tuberculous peritonitis. In general 50ml. of fluid is centrifuged and the pellet is cultured. The sensitivity of culture is only 50%. In contrast laparoscopy with histology and culture of peritoneal biopsies gives a sensitivity of nearly 100% [18].

CYTOLOGY

Cytology should only be expected to detect malignancy when tumor cells line the peritoneal cavity (peritoneal carcinomatosis). Cytology was reported to be only 58-75% sensitive in detecting malignant ascites.

Cytology should not be expected to detect tumor when the peritoneum is not involved as in hepatoma or massive liver metastases causing portal hypertension and resulting ascites or malignant lymphoma causing ascites by lymphatic obstruction. A recently published study that did involve a gold standard diagnosis regarding the location and type of tumor causing ascites formation has shown that only about two thirds of patients with malignancy related ascites have peritoneal carcinomatosis.

Therefore the cytology is approximately 100% sensitive in detecting peritoneal Carcinomatosis but doesn't detect all ascites due to cancer. Because hepatoma rarely metastasis to the peritoneum, the cytology is almost never positive.

Cytogenetic analysis of cells of body fluids for chromosomal criteria in malignancy has yielded more accurate diagnosis with less number of false negative cases in contrast to simple cytological study, a study was conducted, by Bousfield, Greenberg, and Pacey with 50 cases suspected to have cancer by examining body fluids by cytogenetic techniques. There were no false positive results in any of the 16 cases reported positive for malignancy. 23 of the 24 negative cytogenetic reports proved to be accurate [19].

BIOCHEMICAL INVESTIGATIONS

GLUCOSE

The glucose molecule is small enough to diffuse readily into body fluid cavities, therefore the ascitic fluid glucose concentration is similar to that of serum unless glucose is being consumed by ascitic fluid white cells or bacteria [12].

The ascitic fluid glucose is decreased to a moderate degree (50-80mg/dl) in patients with tuberculous peritonitis and peritoneal carcinomatosis. However in SBP detected late and in the setting of gut perforation into ascitic fluid, the glucose level usually drops to zero mg per deciliter because of consumption by stimulated neuturophils and bacteria.

In 1972, diagnostic criteria for most exudates was proposed by light et al [39].

A pleural fluid LDH > 200 units/L

A fluid to serum protein ratio > 0.5

A fluid to serum LDH ratio > 0.6.

LACTATE DEHYDROGENASE (LDH) AND LDH RATIO

LDH enters ascitic fluid by diffusion from blood and also by release from disintegrating ascitic fluid white cells. The ascitic fluid concentration of LDH is usually less than half the serum level in uncomplicated cirrhotic ascites. In spontaneous bacterial peritonitis, the ascitic fluid LDH level rises because of neutrophil release of LDH, such that the ascitic fluid concentration

may be greater than that of serum. In secondary peritonitis LDH level may be even seven fold higher than that of serum [12].

In ascites, serum LDH ratio is also helpful in determining whether the ascites is exudative (Ratio > 0.6) or transudative (Ratio < 0.6) L.

AMYLASE

The ascitic fluid amylase concentration in uncomplicated cirrhotic ascites is usually half that of the serum value, approximately 50 IU/L. In patients with pancreatitis or gut perforation with release of luminal amylase into fluid, the ascitic fluid amylase concentration usually greater than 2000 IU/L [12].

TRIGIYCERIDE

Triglyceride level should be measured in opalescent or frankly milky ascitic fluid. By definition, chylous ascites has a triglyceride concentration of more than 200mg/dl, and greater than the serum level. Usually the level is greater than 1000 mg/dl. A slightly, cloudy cirrhotic sterile ascitic fluid may have an elevated triglyceride concentration 64 ± 43mg/dl compared with 18 ± 9 mg / dl of clear cirrhotic ascites [12].

CARCINOEMBRYONIC ANTIGEN, Alpha – FETOPROTEIN

Carcinoembryonic antigen (CEA) in ascitic fluid has been proposed as a helpful test in detecting malignant ascites. More studies with sub grouping of

patients and good sensitivity and specificity are required before ascitic fluid carcinoembryonic antigen can be considered validated as a useful test [12].

SERUM-ASCITES ALBUMIN GRADIENT (SAAG)

Before 1980, the ascitic fluid total protein concentration was used to classify ascites into transudate (< 2.5gm/dl) and exudates (>2.5gm/dl) The assumption was that the fluid that exuded from inflamed or tumor-laden peritoneum would be high in protein and that transuded from normal peritoneum in the setting of an imbalance of starling forces would be low in protein, unfortunately these assumptions were not entirely correct [12].

The serum-ascites albumin gradient (SAAG) has been proved in multiple studies to categorize ascites better than the total protein concentration and better than other parameters. The SAAG is based on the oncotic-Hydrostatic balance. Portal hypertension results in an abnormally high hydrostatic pressure gradient between the portal bed and ascitic fluid. There must be similarly large difference between ascitic fluid and intravascular oncotic force. Albumin exerts more oncotic force per gram than other proteins. The difference between serum an ascitic fluid albumin concentrations correlates directly with portal pressure.

Calculating the SAAG involves measuring the albumin concentrations of serum and ascitic fluid and simply subtracting the ascitic fluid value from the serum value. Unless there is laboratory error the serum value is always higher, it is a subtraction, not a ratio. If SAAG is greater than 1.1gm/dl the patient has portal hypertension with approximately 97% accuracy. Also if the serum albumin- Ascitic fluid total protein difference is 1.1gm/dl or more, the patient has portal hypertension, since ascitic fluid albumin cannot be greater than ascitic fluid total protein, conversely if the SAAG is less than

1.1gm/dl the patient does not have portal hypertension, with approximately 97% accuracy. If the SAAG is performed properly the accuracy approximates 100% [12].

In the largest series reported (involving 901 paired specimens) accuracy was 96.7%. This test is accurate despite ascitic fluid infection, diuresis, therapeutic paracentesis, albumin, infusion, and etiology of liver disease.

Very rarely a cirrhotic patient can have serum albumin levels <1.1gm/dl. So that the gradient will be falsely low.

The specimens should be obtained on the same day, preferably within the same hour. Both serum and ascitic fluid albumin concentration change in parallel such that the difference is stable.

Peripheral hyperglobulinemia (> 5gm/dl) leads to a high ascitic fluid globulin concentration and can narrow the SAAG by contributing to the oncotic forces. To correct SAAG in the setting of a high serum globulin level, the uncorrected SAAG is multiplied by 0.21 + 0.2 x- serum globulin concentration.

The albumin gradient also remains high in mixed ascites reflecting the underlying portal hypertension.

The presence of a high albumin gradient does not diagnose cirrhosis, it simply indicates the presence of portal hypertension. There are other causes of portal hypertension other than cirrhosis like heart failure. The high SAAG in cardiac failure ascites is presumably due to the high right sided heart

pressures and the fact that the SAAG measures the absolute portal pressures which is increased when the right sided heart, pressure is high. Although peritoneal carcinomatosis is the most common cause of a low albumin gradient there are other causes like tuberculos peritonitis, pancreatic ascites, nephrotic syndrome and the bile leak [12].

In a study conducted with 85 patients with ascitis of various causes by Albillos et al [28] a serum-Ascitic albumin gradient less than 1.1gm/dl was the most accurate parameter for the diagnosis of malignant ascites with a diagnostic efficiency of 93% [28].

Hedenberg et al in Sweden in his study with two groups of patients with cirrhotic and malignant ascites found that ascitic fluid albumin values were only 25% of the serum values in cirrhotic ascites and albumin values were higher in malignant ascitic fluid [29].

Marshall and vogel of Dakota in their study concluded that SAAG value less than 1.1gm/dl similar to malignant ascites occurs in tuberculous ascites also [30].

When 24 patients with non-alcoholic liver disease and 11 with alcoholic liver disease underwent, liver transplantation their portal venous pressure (PVP) and corrected portal venous pressure (PPc) were measured directly by Kajani M.A. et al. 37 and compared with their serum-ascites albumin values. They found that SAAG and PPc are statistically related to each other in individuals with alcoholic liver disease but not in those with non-alcoholic cause of cirrhosis. It was also found that SAAG less than 1.1gm /dl is not

diagnostic of malignancy but can occur in those with advanced non-malignant hepatic disease [31].

Mauer.K.Manxione N.C. of Broux : in New York studied 46 patients with ascites of different causes and found out following points [32].

- SAAG is a reliable indicator of transudative ascites, the so called portal hypertensive ascites.
- Malignant ascites without liver metastasis had features of non-portal hypertensive ascites and SAAG confirmed this.
- The characteristics of malignant ascites associated with liver metastases however resembled those of the portal hypertensive ascites.
- This new parameter (SAAG) is also helpful in distinguishing congestive cardiac failure with high protein ascites from malignant ascites without liver metastasis.
- Myxoedematous ascitic fluid classically categorized as exudative, had an SAAG greater than 1.1gm/dl indicating the possible role of portal hypertension in the development of ascites in these patients.

In a study by Gomez Lechon involving 69 patients with malignant and non-malignant ascites, SAAG below 1.1gm/dl had an accuracy of 94% in separating these two ascites [33].

According to Rector WG Jr and Reynolds T.B., the serum-ascites albumin difference has superior discriminatory power and should replace the ascites total protein concentration in the routine diagnostic examination of

ascites because he found that the serum-ascites albumin difference was large in patients with transudative ascites (1.6 ± 0.5 gm/dl) and small in patients with exudative ascites (0.6 ± 0.4 gm/dl) [34].

In the study by Pare, Talbot, and Hoefs, SAAG was 0.72 ± 0.3 for malignant ascites and 1.8 ± 0.4 for ascites with liver diseases [22].

In another study by Runyon, Hoefs and Morgan the conclusions were as follows [35]:

- Patients with peritoneal carcinomatosis but without massive liver metastases had a uniformly positive ascitic fluid cytology, high ascitic fluid protein, and a low SAAG.
- Those with peritoneal carcinomatosis and massive liver metastasis had a uniformly positive ascitic fluid cytology variable protein concentration, high SAAG and a markedly elevated serum alkaline phosphatase.

Patients with hepotocellular carcinoma superimposed on cirrhosis, had negative ascitic fluid cytology, low ascitic fluid protein concentration, high SAAG and an elevated serum and ascitic fluid ∝Fetoprotein concentration.

MATERIALS AND METHODS

MATERIALS AND METHODS

SELECTION OF CASES:

In this study 100 cases were selected randomly in patients who presented with ascites and got admitted in the medical wards. After clinical Diagnosis, diagnostic paracentesis and ultrasonogram were done to confirm the same in all cases in this study.

PERIOD OF STUDY:

This study was conducted during the period of two years- October 2006 to October 2008.

METHODS:

A detailed history and clinical data was collected using the proforma.

The following investigations have been done in all the patients in this study.

Blood complete hemogram, Random Blood Sugar, Blood Urea, Serum Creatinine, Serum Sodium, Serum Potassium, Urine Albumin, Urine Sugar, Deposits, X-ray Chest PA view, ECG, USG abdomen, Liver function tests, Ascitic Fluid Analysis (bio chemical analysis and cytology) , UGI Scopy.

Other special investigations like echocardiogram, 24hrs urine protein, Serum amylase, Ascitic fluid amylase, Serum α feto - protein,

Adenosine deaminase etc. were done in selective cases whenever needed as follows,

Along with Ascites if the clinical picture was suggestive of heart disease, Echocardiogram was done.

In addition to ascites if the clinical picture was suggestive of nephrotic syndrome, 24hrs urine protein and serum lipid profile done.

If the clinical picture was suggestive of malignant ascites, ascitic fluid cytology for malignant cells and α feto-protein were looked for.

Tests and Methods:

- Blood sugar estimated by Glucose oxidase- peroxidase method.
- Blood urea estimated by Bertheld method.
- Serum creatinine estimated by Jaffe's kinetic method.
- Serum Na+ and serum K+ estimated by flame photometer.
- Serum bilirubin estimated by Malloy Evelyn method.
- Serum protein estimated by Biuret method.
- ALT estimated by kinetic method- IFCC.
- AST and Alkaline phosphatase estimated by kinetic method.
- Ascitic fluid Glucose estimated by GOD POD method.

- Ascitic fluid protein estimated by Sulpho-salicylic acid method.
- Serum amylase and ascitic fluid amylase estimated by kinetic method.
- 24 hrs Urine protein estimated by sulpho-salicylic acid method.

RESULTS AND OBSERVATIONS

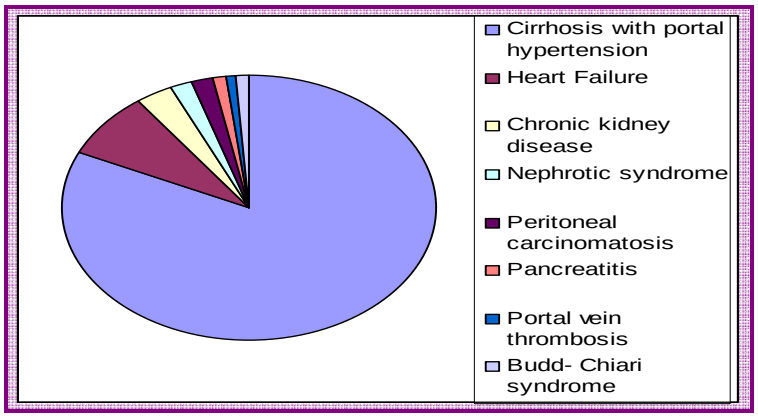
RESULTS AND OBSERVATIONS

In this study of 100 cases of ascites, the etiology and its incidence is observed as,

TABLE I

S.NO	ETIOLOGY	NO. OF CASES	% OF CASES
1.	Cirrhosis with portal hypertension	82	82
2.	Heart Failure	8	8
3.	Chronic kidney disease	3	3
4.	Nephrotic syndrome	2	2
5.	Peritoneal carcinomatosis	2	2
6.	Pancreatitis	1	1
7.	Portal vein thrombosis	1	1
8.	Budd- Chiari syndrome	1	1
Total number of cases		100	100

Chart -1



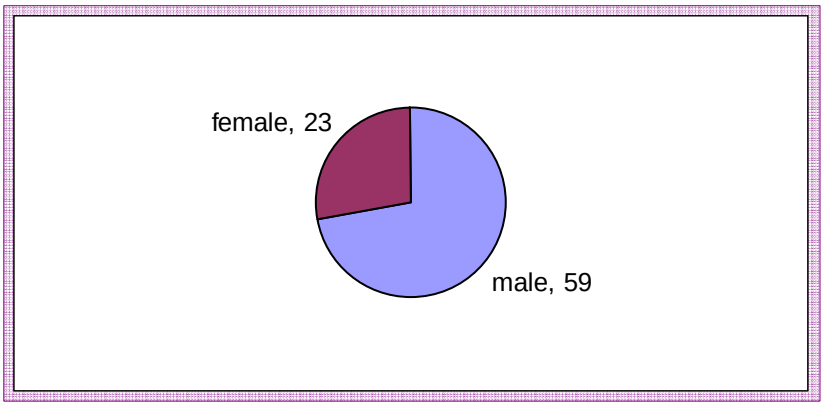
- Cirrhosis with portal hypertension is the most common cause for ascites.

Sex distribution in cirrhosis of liver observed as below:

Table 2

	Number of Cases	%
MALE	59	71.05
FEMALE	23	28.05%
TOTAL	82	100%

Chart -2



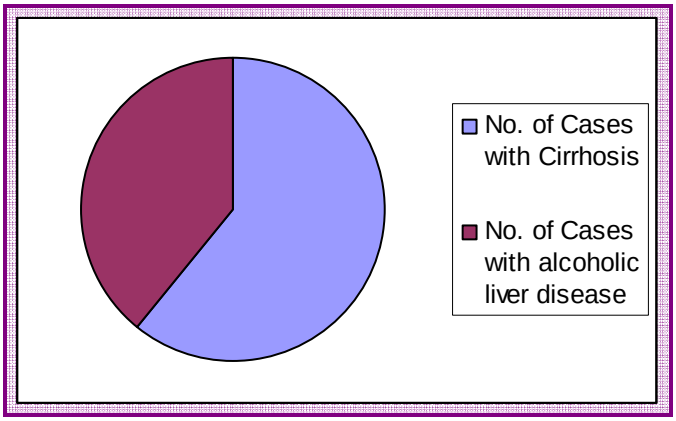
- Cirrhosis of liver is common in males.

The role of alcoholism in cirrhosis of liver observed as:

Table 3

No. of Cases with Cirrhosis	82
No. of Cases with alcoholic liver disease	53
% of Cases	64 %

Chart -3



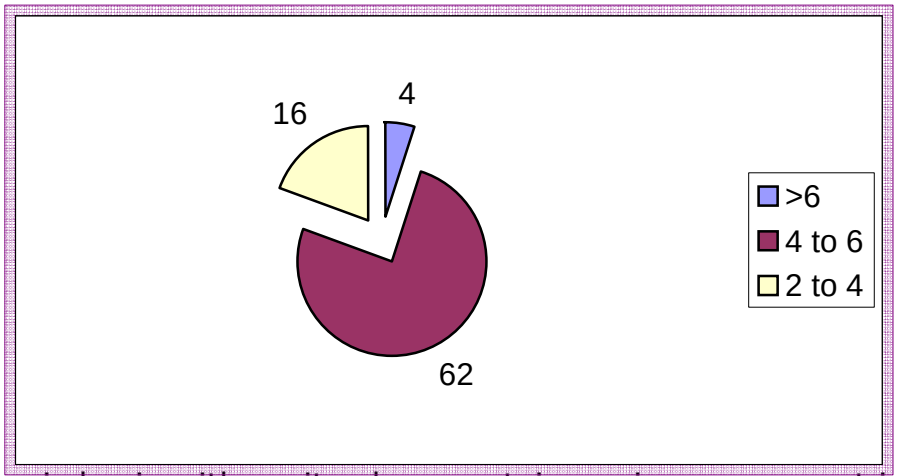
- Alcoholic liver disease is the commonest cause for cirrhosis.

Serum protein value in cirrhosis with ascites:

Table 4

SERUM PROTEIN gms/dl	NO. OF CASES	%
>6	4	4.87
4-6	62	75.60
2-4	16	19.53
TOTAL	82	100

Chart -4



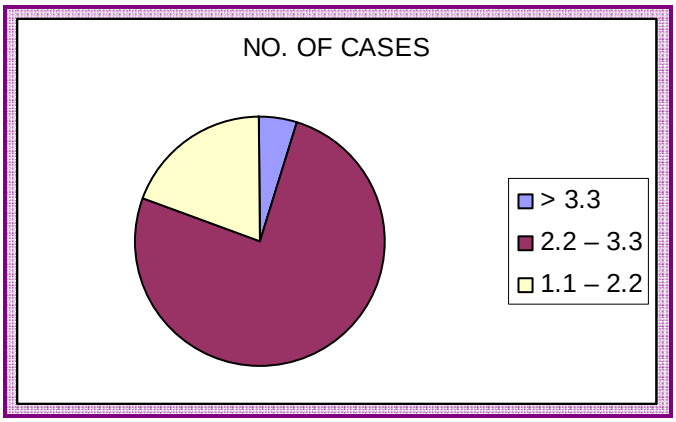
- In cirrhosis with ascites hypoproteinaemia was present in 95 % of cases.

Serum albumin level in cirrhosis with ascites:

Table 5

SERUM ALBUMIN gms/dl	NO. OF CASES	%
> 3.3	4	4.87
2.2 – 3.3	62	75.60
1.1 – 2.2	16	19.53
TOTAL	82	100

Chart -5



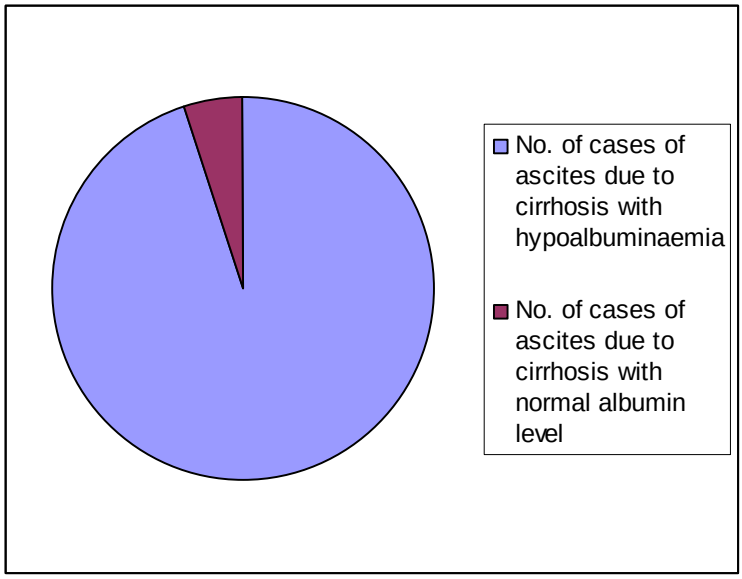
- In cirrhosis with ascites hypoalbuminaemia was present in 95 % of cases.

The incidence of hypoalbuminaemia in cases of cirrhosis with ascites:

Table 6

No. of cases of ascites due to cirrhosis with hypoalbuminaemia	78	95 %
No. of cases of ascites due to cirrhosis with normal albumin level	4	5 %
Total no of cases of ascites due to cirrhosis	82	100 %

Chart -6



- In cirrhosis with ascites hypoalbuminaemia was present in 95 % of cases.

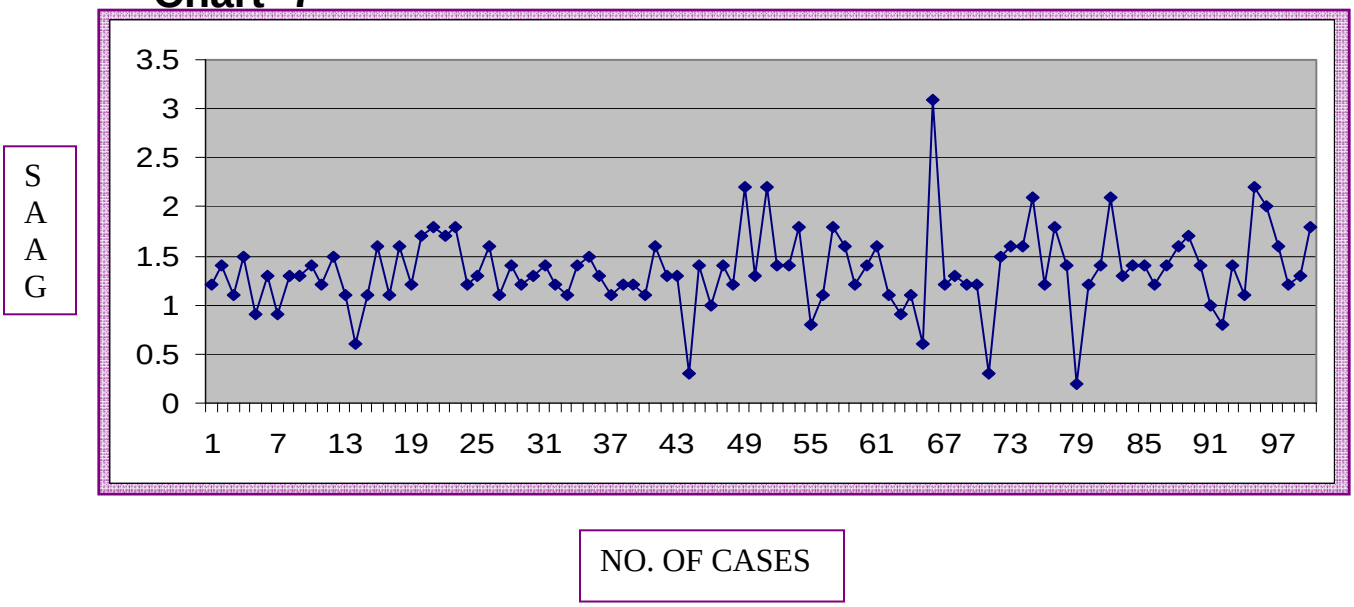
In this study in cases of cirrhosis with portal Hypertension

SAAG value is observed as:

Table 7

SAAG	No. of cases	%
>1.1	76	92.6
<1.1	6	8.4

Chart -7



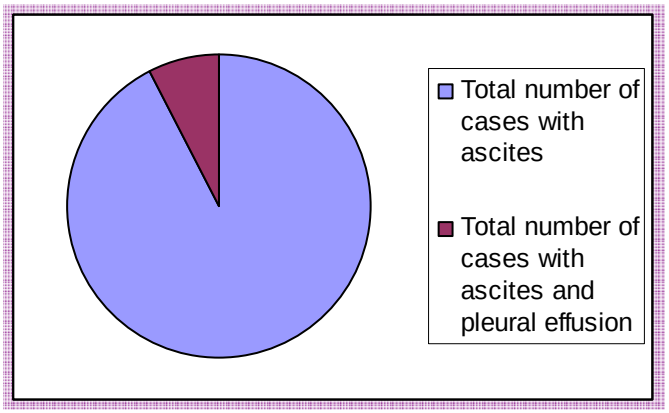
- In cirrhosis with portal hypertension SAAG value is more than 1.1 in 92.6 % of cases.

In this study incidence of pleural effusion along with ascites as follows,

Table 8

Total number of cases with ascites	100
Total number of cases with ascites and pleural effusion	8
% of cases	8

Chart - 8



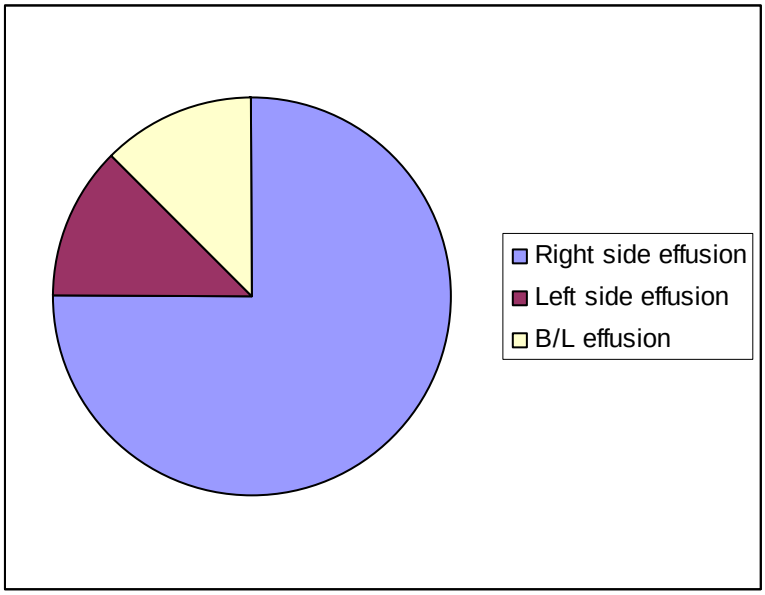
- In cases of ascites, pleural effusion was present only in 8 % of cases and the effusion was common in right side.

In this study in cases of ascites, side of the pleural effusion observed as :

Table 9

Right side effusion	6	75 %
Left side effusion	1	12.5 %
B/L effusion	1	12.5 %
Total number of cases	8	100 %

Chart -9



- In ascites pleural effusion is common in right side.

The incidence of portal hypertension in cases of ascites due to cirrhosis:

Table 10

No. of cases of ascites due to cirrhosis	82 cases
No. of cases of ascites due to cirrhosis with portal hypertension	82 cases

- Portal hypertension was present in all the cases of ascites due to cirrhosis.

DISCUSSION

DISCUSSION

1. In this study of 100 cases of ascites, the etiology and its incidence is observed as,
    1. Cirrhosis with portal hypertension 82%
    2. Heart Failure 8 %
    3. Chronic kidney disease 3 %
    4. Nephrotic syndrome 2 %
    5. Peritoneal calcinomatosis 2 %
    6. Chronic pancreatitis 1 %
    7. Portal vein thrombosis 1 %
    8. Budd-Chiari syndrome 1 %

Cirrhosis with portal hypertension was the most common cause for Ascites and Heart failure was the second most common cause of ascites. This coincides well with the following two studies,

a) The study of Runyon BA, Montano AA, Akriviadis EA et al [35], the etiology and its incidence for ascites is as follows,

1. Cirrhosis with portal Hypertension 85 %
2. Miscellaneous portal hypertension 8 %
3. Cardiac disease 3 %
4. Peritoneal Carcinomatosis 2 %
5. Miscellaneous normal HT related disorders 2 %

b) The Study of Vicente Arroyo, Pere Gines, Ramon planas, Juan Roodes et al[2] the etiology and its incidence for ascites is as follows, hepatic

cirrhosis 88 % neoplasms 6% and to a lesser extent congestive heart failure 3 %, tuberculous peritonitis 2 % and other 1 %.

2. In this study, of the 82 cases of cirrhosis with portal hypertension, 59 cases were male and 23 cases were female. Of the 59 male cases 44 cases were alcoholics – alcoholism is the commonest cause for cirrhosis with portal HT in male. This coincides well with the study of the Tuyns A PequignotG: Greatest risk of ascitic cirrhosis in males in relation to alcohol consumption Int J Epidemiol 13:53, 1984 [40].

3. Chronic pancreatitis was the cause for ascites in one case of Ascites, and alcoholism was the cause for pancreatitis. In the study of Norton J Green berger, alcoholism was the commonest cause for pancreatitis [11].

4. In this study along with ascites, pleural effusion was present in 8 cases (8 %) of ascites.

5. Of the 8 cases, 6 cases presented with Right sided effusion (75 %), 1 case presented with Left sided effusion (12.5 %), 1 case presented with Bilateral effusion (12.5 %). In the study of Leuallen EC, Carr DT, 4.8 % cases of cirrhosis with portal HT were having Pleural effusion and majority of cases 90 % were having Right sided Pleural effusion, 7 % were having Bilateral effusion 3 % having Left sided pleural effusion [36].

6. In cirrhosis with Portal hypertension, serum protein ranges between 2 – 6 grams. 75.6 % have 4 – 6 grams, 19.5 % have 2 – 4 grams, 5 % have > 6 grams, and 5 % cases have normal protein value. In the study of Runyon total ascitic protein concentration ranges between 0.5 grams and

more than 6 grams and is greater than 3 grams in up to 30 % of patients with other uncomplicated ascites [37]. In the study of Runyon, the proportions of albumin and globulin in the total protein concentration are approximately 45 and 55 % respectively and the value ranges between 0.225 grams to 2.7 grams [37].

7. In cirrhosis with Portal hypertension, serum albumin values ranges between 1.1 grams to 3.3 grams. In the study of Runyon, the proportions of albumin and globulin in the total protein concentration are approximately 45 and 55 % respectively and the value ranges between 0.225 grams to 2.7 grams [37].

8. 5 % of cases had normal protein and albumin and these cases presented with ascites, in those cases portal hypertension was present which was evident by oesophageal varices. So the cause of ascites in those cases was portal hypertension.

9. In this study in cirrhosis with Portal hypertension 76 cases (93.7 %) were having SAAG value more than 1.1, 6 cases (6.3 %) were having SAAG value less than 1.1 . This coincides with the study of Runyon BA, Montano AA, Akriviadis EA et al where SAAG value was more than 1.1 in 97 % cases of Cirrhotic ascites and less than 1.1 in Non cirrhotic ascites [35].

10. In this study, 8 cases of ascites were caused by heart failure. Of which 5 cases (62.5 %) were caused by CAHD and 3 cases (37.5 %) were caused

by Rheumatic heart disease. In the study of Eugene Braunwald, CAHD followed by RHD are the common causes of heart failure [9].

11. In heart failure, 6 cases (75 %) had Ejection fraction < 60 % and 2 cases (25 %) had an ejection fraction > 60 % and both of these cases were caused by RHD.

In the study of Rick a Nishimura, Raymond J Gibbons, James F, Glockner, A Jamil Tajik, Ejection fraction usually less than 60 % in Left ventricular failure [38].

CONCLUSION

CONCLUSION

1. This study shows Cirrhosis with portal hypertension was the most common cause for ascites (82 %) and the next common cause for ascites was heart failure (8 %) followed by renal diseases (5 %) – chronic kidney disease, nephrotic syndrome and other rare causes including peritoneal carcinomatosis, portal vein thrombosis, budd-chiari syndrome all together were 5 % only.

2. In this study 79 % of ascites were found to be high gradient ascites and 11 % were low gradient ascites.

3. In this study portal hypertension was present in all the case of ascites due to cirrhosis, as evidenced by oesophageal varices in UGI scopy, where as hypoproteinaemia was present only in 95 % which shows portal hypertension is the major cause for ascites in Cirrhosis.

4. In cirrhosis with portal hypertension alcoholic liver disease was the commonest cause (64 %).

5. Among alcoholics in one case the ascites was due to pancreatitis and not due to cirrhosis of liver.

6. Among the renal causes for ascites which was 5 %, the incidence of chronic kidney disease (3 %) and nephrotic syndrome (2 %) were almost same.

7. In this study malignant ascites was only 2 %.

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PROFORMA

Name: **Age:** **Sex:** **IP No.:**

Address:

Clinical Summary:

Investigations:

HB: **Urine Albumin:**

TC: **Urine Sugar:**

DC:

Random Blood Sugar: **X-Ray Chest PA view:**

Blood Urea:

Serum Creatinine: **E.C.G:**

Serum Na+:

Serum K+: **USG Abdomen:**

UGI Scopy:

Liver Function Test	Ascitic Fluid Analysis
Serum Bilirubin:	**Gross Appearance:**
Total:	**Glucose:**
Conjugated:	**Protein:**
Unconjugated:	**Albumin:**
Serum Protein:	**SAAG:**
Total:	**Cytology:**
Albumin:	**Smear for Gramstain (when needed)**
Globulin:	**Culture and Sensitivity (when needed)**
ALT:	
AST:	
Alkaline Phosphatase:	

Others (When needed)

Echocardiogram:

Serum amylase:

Ascitic fluid amylase:

24 hours urine protein:

Adenosine deaminase: